SUMMARY STATEMENT

PROGRAM CONTACT: [redacted]

(Privileged Communication)

Release Date: **10/23/2018**
Revised Date:

Application Number: **2 R01 DC003687-22A1**

Principal Investigator

SHERA, CHRISTOPHER A

Applicant Organization: [redacted]

Review Group: **AUD**
Auditory System Study Section

Meeting Date: **10/11/2018**
Council: **JAN 2019**
Requested Start: **04/01/2019**

RFA/PA: **PA18-484**
PCC: **HR50**

Project Title: **Understanding Otoacoustic Emissions**

SRG Action: **Impact Score:20 Percentile:3**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **3A-No children included, scientifically acceptable**

Project Year			
22	[redacted]	[redacted]	[redacted]
23			
24			
25			
26			

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.
BUDGET MODIFICATIONS

2R01DC003687-22A1 SHERA, CHRISTOPHER

COMMITTEE BUDGET RECOMMENDATIONS

RESUME AND SUMMARY OF DISCUSSION: This well-written resubmitted renewal R01 application from an established investigator aims to address important unresolved issues in cochlear mechanics and further develop the theoretical underpinning to help with interpretation of experimental otoacoustic emissions (OAEs) data. The scientific significance of the proposed research is very high, and the use of the combination of experimental and modeling approaches was viewed positively by the reviewers. The approach to the OAE acquisition protocol to decrease the testing time could be clinically applicable, particularly for pediatric populations. The principal investigator (PI) is a leader in the field of OAEs, well positioned to carry out the work. He was extremely productive in the previous grant cycles, adding to the strength of this competing renewal. The research team has considerable experience in obtaining OAEs in humans, and the collaboration with [redacted] to study the mechanics in the mouse cochlea further instills confidence of success. This resubmission was largely responsive to the prior critiques by modifying one of the aims. However, the response to the lack of description of statistical approach is unsatisfactory, slightly diminishing the enthusiasm for some reviewers. Nevertheless, the panel concluded that this strong application will likely have long-term high impact in enhancing our basic understanding of cochlear mechanics with potential translational application to improve OAE measures in clinical settings.

DESCRIPTION (provided by applicant): Realizing the potential of otoacoustic emissions (OAEs) as noninvasive probes of cochlear function requires understanding the physical and physiological mechanisms that generate and shape these sounds. To address important unresolved issues of cochlear mechanics while improving our understanding of OAE generation, we propose three aims involving innovative theoretical modeling rigorously tested by experimental measurements. The first Aim studies the action of “suppressor” tones on OAE generation by testing the hypothesis that suppressors can both reduce the strength of existing OAE sources and create new sources of wave reflection within the cochlea. We determine whether suppressors can accurately map out the distribution of OAE generators in models where the distribution is known in advance and test whether eliminating sources created by the suppressor can improve the measurement of cochlear frequency selectivity using OAE suppression tuning curves. The second Aim studies the nature of the micromechanical irregularity believed necessary for the generation of reflection-source OAEs. We test whether efferent-induced changes in OAEs can be explained by the hypothesis that activation of medial olivocochlear (MOC) efferents alters the spatial pattern of irregularity. Using both measurements and models, we also explore the hypothesized but previously unrecognized role of irregularity on the generation of distortion-source OAEs and its modulation by contralateral acoustic stimulation. The third Aim explores the micromechanics of cochlear wave amplification and its consequences for OAE generation. Modeling work studies OAE generation in models incorporating forms of spatial feed-forward/backward amplification suggested by the oblique geometry of the outer hair cells. We also combine state-of-the-art measurements of organ of Corti vibration using optical coherence tomography (OCT) with theoretical inverse methods to study how the assumed coupling between the modes affects the generation and propagation of OAEs. Completion of these Aims will significantly enhance our understanding of OAE generation and its relationship to cochlear mechanics. The Aims are also directly relevant to improving the power of OAE-based diagnostics and other technological applications—such as hearing aids and preprocessors for speech-recognition devices—that benefit from knowledge of cochlear amplification, nonlinearity, and signal processing.

PUBLIC HEALTH RELEVANCE: Our experiments and models address the mechanisms by which healthy ears generate sound. Sounds from the ear, known as otoacoustic emissions (OAEs), are widely used for noninvasive tests of hearing function. By improving our understanding of how OAEs are produced within the cochlea, and how they can be used to probe aspects of cochlear function important

for human communication, the proposed work will enhance the power of clinical hearing tests and help improve the design of auditory prosthetic devices.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 4
Environment: 2

Overall Impact: This is an excellent proposal from a productive PI whose techniques and strategies have driven the OAE field for many years. Overall, the project seeks to enrich our understanding of OAEs by (1) carefully studying the nonlinear interactions that occur during SFOAEs under different suppression paradigms especially those that speed acquisition (2) study the possibility that “irregularity” (and this could be from outer hair cells (soma, HB), material parameters, or other sources) could give rise to time varying (dynamic) effects (3) study the possible influence of new concepts in mathematical modelling of the cochlea ((a) spatial feedforward of gain – feedback of elastic properties) and (b) multimodal structure-fluid waves (coupled to the BM and TM)) on the interpretation of OAEs (do these new findings upset any of the tenets used in analyzing the data).

Collaborations with experts in VOCTV will be used to inform the model and provide state-of-the-art interpretations of OAEs. They seek to address a key new question – do OAEs correlate more with RL motion than BM motion.

A strength of the application is to combine an excellent team for measurements of OAEs in humans and mice with nonlinear analytic modeling for interpretation of the data. This is especially important when interpreting different protocols for SFOAE analysis, the model will inform the community as to approach with a known dynamical. This research will develop a theoretical framework to better understand OAEs and better clinical procedures (faster and reliable).

The application is focusing on new mechanisms and model correlations. Hence potential sex differences and statistical power are not as critical as they would be for comparisons between interventions, for instance, which are not being made. Further, we expect the basic mechanics of, say, multimodal behavior, to be the same in males and females. Statistical rigor for measurements is still a weakness. The application would be improved if a better (brief) discussion of statistics of the number of subjects needed to get reliable (within variance) results. Both sexes used and will be examined for differences (not statistically powered). However, in humans females are preferred because of higher OAEs.

1. Significance

Strengths

- The scientific premise of this work is strong – understanding how to interpret otoacoustic emissions is important because of its noninvasive and quantitative nature. However, the source of the emissions, causes for variability, and interpretation of the data (delays, amplitudes) are still open issues as is the need for the development of clinically efficient techniques (with regard to time and repeatability of the measurements). The premise of Aim 1 is strong.
- Two-tone suppression and interaction require a more complete understanding, especially as applied to OAEs. SFOAEs are complex (protocols) – the question of do suppressors always suppress will be addressed.

- Aim 3a is added/altered to address critiques to not only look at other aspects of micromechanics that may give rise to
- Aim 3b has been changed in name (still essentially testing the hypothesis of van der Heijden) but it still is mainly looking at this idea of the correlating of structures other than the BM with OAE. The collaboration with Oghalai enables the PI makes this possible. They seek to address the question of correlation of OAEs with RL motion rather than BM motion. This is important to do as the BM-only view of the cochlear mechanics is now disrupted and we are coming closer to understanding the mechanics by which the ANF tuning curves and other physiologically important measures (as well as OAEs) may differ from BM motion.
- The notion of a “dynamic” component of irregularity is interesting and could lead to an understanding of the source of irregularities causing scattering. (Aim 2)
- If this work is successful, the connection between OAEs and sensorineural hearing loss and noninvasive tuning measures will be more secure.
- This work should be done to move this field forward from a theoretical, clinical, and methodological standpoint.

Weaknesses

- Using MOC and MOC irregularity to probe irregularity will present confounding result (both are posited to be irregular).
- Aim 2 is weakened because there is no mechanistic hypothesis for the dynamical nature of the irregularity (is it HB related/OHC somatic related) and a discussion of how it might be determined is missing.

2. Investigator(s)

Strengths

- Shera is a leader in the analysis (analytic and via signal processing) of OAEs. His methods have influenced interpretation of this important clinical tool worldwide.
- The team is outstanding and very complementary with all important areas (OAE measurements in the clinic; OCT measurements; MOC stimulation) covered.

Weaknesses

- Very little discussion of an interaction plan justifying all parties’ involvement (the work is there to do - but some discussion of the interaction plan is missing).

3. Innovation

Strengths

- Studying wave anisotropy in models due to feedforward/feedback mechanisms while relating them to OAEs is innovative (with the hypothesis that such mechanisms may not be consistent with OAEs).
- Irregularities having a “dynamic” component (that might be indicative of placement of the irregularities in the HB or OHC soma).
- Including VOCTV measurements to analyze the correlate of mechanics of different structures to OAEs and compare latencies in OAEs to putative intracochlear generators.
- Using MOC to see if reducing the effectiveness of OHCs can increase the emission is innovative.

Weaknesses

- None noted.

4. Approach

Strengths

- The use of complementary models (Shera versus Liu and Neely models) is a strength (needed to study 3b) and the use of simplified (phenomenological) models like this is important for all aims. This is especially true for Aim 1, where these models can provide a relatively simple platform to test algorithms (swept protocols) for experiments. These models are important because they show potentially important wave phenomena that can be linked to mechanism for each effect.
- The CWT approach put forth in Bergevin and Shera uses advanced and efficient signal processing as well as the recognition (often not mentioned) that reflections will confound the delay measurements and must be taken into account – great that this is proposed.
- Relatively simple model allows for rapid and controllable variation of the model and for nonlinear simulations in the time domain to be used.
- Sex as a biological variable is addressed – but downplayed.

Weaknesses

- Modeling details not spelled out – making them hard to evaluate. “Strategic simplifications” (otherwise known as either modeling assumptions or hypotheses about the central structures necessary for modeling) are mentioned but not specified. Elastic coupling by the TM is mentioned not to be important – but it has already been shown important (models and experiments – Russell ... Richardson (2007)) – especially around the best place – so some of the model concepts still need to be settled for the multicomponent model (aim 3b) to test OCT measured RL responses.
- The irregularity hypothesis testing is still troublesome because it is difficult to validate physiologically (although it is supported now by several models) – the notion that spotty (irregular) MOC activation plus static irregularity could predict increased OAE under MOC stim (which should reduce the OAE because of reduced OHC activity) seems to compound two uncertain (and difficult to verify experimentally) contributors. I’m concerned that this may be unproductive because of the confounding nature.
- For two-tone interaction (suppression) there are interactions at the level of the suppressor interacting with the probe tone more than just at each tone’s primary frequency (i.e., there are distortion products). The effect of this nonlinearity is not discussed – even though it will be present in their model.
- Statistics of obtaining reliable experimental data are not clearly described – while mentioned it’s not very clear. They plan to utilize sufficient animals until significance is attained (with initial estimates based on past experience).

5. Environment:

Strengths

- For all components; an excellent environment is in place to perform these experiments.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

YES, all criteria addressed

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- Generally, addresses previous critique.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Budget Modifications Recommended (in amount/time)

Recommended budget modifications or possible overlap identified:

- The budget seems high - work could be done with one fewer post-doc.

CRITIQUE 2:

Significance: 2
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: Otoacoustic emissions (OAEs) constitute a powerful noninvasive window on the mechanics of the cochlea. OAEs provide both valuable assays of cochlear function and unique tools for exploring fundamental issues about how the cochlea works, especially in humans. For example, OAEs have found widespread but diagnostically limited use in audiology clinics and research labs, where they serve primarily to detect (but not to describe) OHC-related hearing loss with roughly half-octave frequency resolution. A more thorough understanding of inner-ear mechanics and emission generation may allow for more widespread clinical applicability of OAEs. Thus, there is high potential significance of the work. The foundational premise of the work is strong and based on prior literature and preliminary data. Additional strengths included the fantastic PI and assembled team, superb progress during the prior grant period, good conceptual innovation, a logical and feasible approach and a strong environment. Weaknesses were few and negligible but did include a general lack of description of

statistical treatment of the data and sample sizes. The weaknesses did not detract from enthusiasm for this proposal.

1. Significance

Strengths

- Otoacoustic emissions (OAEs) constitute a powerful noninvasive window on the mechanics of the cochlea. OAEs provide both valuable assays of cochlear function and unique tools for exploring fundamental issues about how the cochlea works, especially in humans. For example, OAEs have found widespread but diagnostically limited use in audiology clinics and research labs, where they serve primarily to detect (but not to describe) OHC-related hearing loss with roughly half-octave frequency resolution. A more thorough understanding of inner-ear mechanics and emission generation may allow for more widespread clinical applicability of OAEs.
- The premise of the work is that there are several key areas of OAE generation that are likely not correct and could lead to inaccuracies in interpretation of the results – e.g., the role and mechanism of suppressor tones necessary to measure cochlear frequency selectivity. The premise is based on literature and preliminary data including modeling.

Weaknesses

- None noted.

2. Investigator(s)

Strengths

- The PI, Dr Chris Shera, is a leader and pioneer in the study of OAEs. The PI is more than capable of conducting the proposed work.
- Progress during the prior grant period was phenomenal, with at least 27 peer reviewed publications and several review chapters.
- The PI has assembled a stellar team [redacted] to assist with novel measurement using optical coherence tomography (OCT).

Weaknesses

- None noted.

3. Innovation

Strengths

- The combination of experiment and modeling, while commonplace in many proposals, is innovative here due to how tightly the models and experiments are woven together.
- There are several conceptual innovations including focus on OAE components that were once likely thought to be simply sources of noise, including the role of suppressor tones, the role of micromechanical irregularities, and new ideas of how OAEs are modulated by efferent innervation

Weaknesses

- None noted.

4. Approach

Strengths

- As stated by the PI, most of the methodology uses the already innovative and powerful acquisition and analysis techniques that the PI and collaborators have developed over the past several years. The experiments leverage these vetted methodologies to explore new ideas regarding OAE generation.
- There were good preliminary data for most of the more difficult experiments lending confidence that the experiments will bear solid data necessary to test core hypotheses
- In Aim 1 the method proposed to eliminate sources of suppressor tone effects on frequency selectivity estimates by filtering out the short latency components is neat
- The identification and use of a negative delay component in Aim 2 and its use to study biological sources of small micromolecular irregularities is also neat
- Use of OCT to measure displacements of the basilar membrane and reticular lamina and correlate those results with obtained OAEs to study sources of vibrational modes of the organ of corti that might be OAE generators is strong
- Sex as a biological variable was addressed adequately

Weaknesses

- There still remains no power analysis nor statistical methods to rigorously examine the results. The PI suggests that animal and human numbers are based on past experience in the lab. With increased emphasis on methods to bolster rigor and reproducibility this is no longer sufficient.

5. Environment:

Strengths

- The scientific and intellectual environment [redacted] is world class.
- The PI and team have all of the necessary equipment and facilities to conduct the proposed work.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- The proposed use of human subjects is acceptable and necessary for the research. Adequate provisions are in place to protect human subjects from anticipated risks.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically
- Equal numbers of males and females will be recruited. The study achieves a representative mix with regard to ethnic and racial categories based on the representation of these categories [redacted] Children under 18 are justifiably excluded based on task difficulty.

Vertebrate Animals:

YES, all criteria addressed

- Species, strain, sex, age and numbers of animals needed are adequately indicated. Experiments are well justified. Appropriate care is indicated as are procedures to minimize pain and discomfort. Appropriate methods for euthanasia are indicated.

Biohazards:

Not Applicable (No Biohazards)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 2
Investigator(s): 2
Innovation: 3
Approach: 3
Environment: 2

Overall Impact: This is a well-written application proposing experiments to better understand the generation of OAEs through a combination of human data and modelling. The first aim tests the idea that suppressor tones can themselves introduce reflections and offers a procedure for removing these effects. The second aim evaluates possible contributions of dynamic, MOC related changes to the irregularities associated with reflections. And the third aim evaluates the possible role of feed-forward/backward amplification in OAE generation. Experiments address important and fundamental questions about cochlear function. This work is likely to result in concrete tools and procedures for interpreting OAE data, with applications for both clinical and research endeavors. Importantly, results are expected to lead to a re-interpretation of published data (e.g., SFOAE suppression tuning curves). The PI is highly qualified to carry out this work, and the credentials of his Co-investigators further bolster confidence. Progress in the previous funding period was excellent, and response to prior reviews for this resubmission was strong.

The scientific premise is supported by published and pilot data. Rigor is demonstrated via careful consideration of alternative explanations for patterns of data observed, stringent artifact rejection, repeated measurements, comparison of models from other groups, and converging evidence across modeling, behavioral and imaging.

No sex effects are expected, but analyses will be performed to look for them.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Risks are minimal and well controlled.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

- The recruitment plan calls for running equal numbers of males and females, and for a racial/ethnic demographic that reflects the local population. Children are omitted due to the task demands.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Budget and Period of Support:

Budget Modifications Recommended

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION OF CHILDREN PLAN: ACCEPTABLE

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: After discussion, the panel recommended the elimination of one postdoc position.

Footnotes for 2 R01 DC003687-22A1; PI Name: SHERA, CHRISTOPHER A

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

[redacted]